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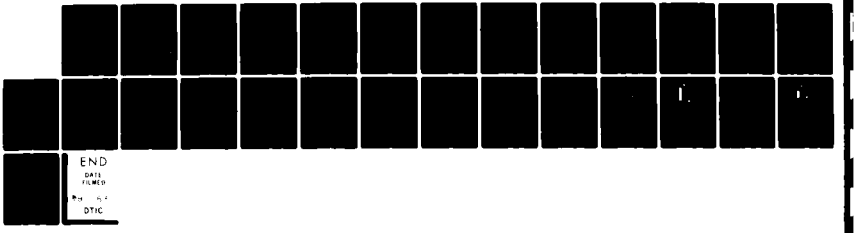

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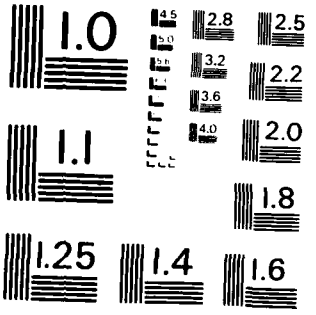

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) Although adrenergic agonists increase resting ventilation and responsiveness to CO_2, there are conflicting data about the effect of adrenergic blockade on ventilatory responses. In this study, we investigated the effect of alpha- or beta-adrenergic blockade on the response to hyperoxic CO_2 rebreathing in awake goats. In five goats, studied before and after intravenous administration of phentolamine or propranolol, there was no difference (compared to control studies) in the mean slope, x-intercept, or ventilation at end-tidal P_{CO_2} (P_{ETCO_2}) = 70 torr for the CO_2 response

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curves after either drug. When mean inspiratory flow rate (V_T/T_i) was plotted against P_{ETCO_2}, there was also no change in these measurements after propranolol. After phentolamine, there was a slight decrease in the slope and x-intercept, but no change in V_T/T_i at P_{ETCO_2} = 70. We conclude that acute administration of alpha- or beta-adrenergic blockers does not affect ventilatory response to CO_2 inhalation in goats, and suggest that adrenergic activity is not an important modulating influence for CO_2 responsiveness in this species.

ADRENERGIC BLOCKADE DOES NOT CHANGE VENTILATORY RESPONSE TO CO_2 IN AWAKE RESTING GOATS

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Running head: Adrenergic Blockade and Ventilatory Response

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Abstract

Although adrenergic agonists increase resting ventilation and responsiveness to CO_2, there are conflicting data about the effect of adrenergic blockade on ventilatory responses. In this study, we investigated the effect of alpha- or beta-adrenergic blockade on the response to hyperoxic CO_2 rebreathing in awake goats. In five goats, studied before and after intravenous administration of phentolamine or propranolol, there was no difference (compared to control studies) in the mean slope, x-intercept, or ventilation at end-tidal P_{CO2} (P_{ETCO2}) = 70 torr for the CO_2 response curves after either drug. When mean inspiratory flow rate (V_T/T_i) was plotted against P_{ETCO2}, there was also no change in these measurements after propranolol. After phentolamine, there was a slight decrease in the slope and x-intercept, but no change in V_T/T_i at P_{ETCO2} = 70. We conclude that acute administation of alpha- or beta-adrenergic blockers does not affect ventilatory response to CO_2 inhalation in goats, and suggest that adrenergic activity is not an important modulating influence for CO_2 responsiveness in this species.

Index terms

Ventilatory control, phentolamine, propranolol

Introduction

Breathing is influenced by a complex interaction of stimuli and modulating factors acting at various levels of the nervous system. These modulating factors include input from the cerebral cortex and presumably from neurohumoral (including hormonal) systems (Eldridge and Millhorn [1981]). There are two ways in which neurohumoral factors could exert an influence on ventilatory control. First, it is possible that the baseline level of activity of the system at the time of testing could influence responsiveness to ventilatory stimuli, such as hypoxia or hypercapnia. Alternatively, the ventilatory stimulus could change activity of the neurohumoral system, thereby indirectly stimulating or inhibiting ventilation through a neurohumoral mechanism.

As part of a broader interest in neurohumoral factors that might affect the regulation of respiration, we wanted to know whether sympathoadrenal activity in the resting animal normally influences ventilatory responsiveness to CO_2. One can postulate several ways in which adrenergic activity might interact with ventilatory control. First, blood flow to chemoreceptors or to medullary respiratory neurons might be affected by the level of adrenergic activity, and changes in responsiveness might be related to altered blood flow to these regions (Lopez de Pablo, et al. [1982]). Another possibility is that adrenergic receptors are present on cells directly involved in respiratory control, either chemosensors or cells included in the pathway for generation of respiratory rhythm. Finally, by changing the level of metabolic activity, i.e. oxygen consumption and carbon

dioxide production, the sympathoadrenal system might influence metabolic input to the respiratory control system and thereby alter ventilatory output.

Several studies using adrenergic agonists suggest that administration of these agents increases resting ventilation and may augment the response to acute hypoxia or hypercapnia (Cunningham, Hey, and Lloyd [1958]; Heistad, et al. [1972]; Joels and White [1968]; Keltz, Samortin, and Stone [1972]; Wasserman, et al. [1979]; Whelan and Young [1953]; Winn, Hildebrandt, and Hildebrandt [1979]). However, demonstration of an effect of exogenous adrenergic agonists on ventilation does not necessarily mean that intrinsic sympathoadrenal activity normally influences ventilatory responsiveness. To establish that possibility, one must either quantitate intrinsic sympathoadrenal activity, or assess the effect of adrenergic blockers on ventilatory responses.

Prior studies on the effect of adrenergic blockers on ventilatory control have produced conflicting results. Most of these studies have been done in humans. After a single dose of the beta-blocker propranolol, the ventilatory response to CO2 inhalation was reported to be either decreased (Mustchin, et al. [1976]; Trembath, et al. [1979]) or unchanged (Hutchinson and Harrison [1980]; Patrick, Tutty, and Pearson [1978]). Similarly, conflicting results were observed after administration of propranolol for several days (Campbell, Lauver, and Cobb [1981]; Hutchinson and Harrison [1980]). In other studies, administration of an alpha adrenergic agonist did not affect basal minute ventilation in humans (Heistad, et al.

[1972]) or the response to hyperoxic CO2 rebreathing in goats (Edelman, et al. [1970]).

To explore further the possibility that the sympathoadrenal system normally plays a role in the regulation of breathing, we assessed the effect of alpha blockade with phentolamine or beta blockade with propranolol on the ventilatory responses of awake goats to CO2 rebreathing.

Methods

Five adult goats (4 males, 1 female) weighing 31 to 58 kg (mean 38.4 kg) were used in all experiments; each animal was studied at rest in the awake, fasted state. All animals had previously been provided with skin-denervated carotid loops. For each study, two plastic cannulas were inserted percutaneously, one into the carotid artery and the other into the contralateral external jugular vein. The arterial cannula was connected to a pressure transducer for continuous monitoring of heart rate and arterial blood pressure, which were displayed on a Brush recorder (Gould model 200). The venous catheter was used for administration of drugs.

Respiratory Measurements

Carbon dioxide rebreathing was performed by a modification of the technique of Read [1967]. A latex rubber mask was fitted snugly over the goat's snout and connected to a three-way T valve through wide-bore tubing (30 cm length, 3.5 cm i.d., Warren E. Collins). One of the remaining ports of the valve was open to air; the other was connected to a rebreathing bag enclosed in a rigid box. The box was connected by wide-bore

tubing (2 m length, 3.5 cm i.d.) to a Wedge spirometer (Med Science model 570). Gas was sampled continuously from the mask at a rate of 60 ml/min, and partial pressures of O2 and CO2 were measured with a mass spectrometer (Perkin-Elmer model 1100A). All measured variables were displayed on the strip-chart recorder and recorded on magnetic tape (Hewlett-Packard model 3968) for later analysis by computer.

Each rebreathing test was started with approximately 5 L of gas (7% CO2, balance O2) in the bag. When end-tidal PCO2 (PETCO2) had been stable for at least 2 minutes with the goat breathing air, the Y valve was turned at end-expiration so that the goat subsequently inspired from and expired into the rebreathing bag. Rebreathing was terminated when PETCO2 reached approximately 75 torr or the goat became restless. Rebreathing tests were performed in triplicate on each goat for each experimental condition.

Experimental Design

Each goat was studied on separate occasions at least 48 hours apart. On each day, three baseline CO2 rebreathing tests were performed at least five minutes apart prior to administration of an adrenergic blocker.

For studies involving alpha adrenergic blockade, phentolamine was administered intravenously with an initial bolus of 3.8 mg followed by a continuous infusion of 0.19 mg/min throughout the rebreathing studies. The first of the three post-phentolamine rebreathing studies was started five minutes after the bolus was given. Following the final post-phentolamine rebreathing study and while phentolamine was

still being infused, an intravenous infusion of norepinephrine (40 µg/min) was administered to assess the effectiveness of alpha blockade in attenuating the pressor response to norepinephrine.

For studies involving beta adrenergic blockade, propranolol (0.15 mg/kg) was administered as a single intravenous infusion over 10 minutes after three control CO2 rebreathing studies. The first of the three post-propranolol rebreathing studies was started 10 minutes after the infusion was completed. Following the final post-propranolol study, isoproterenol (2 µg/min) was infused intravenously to test the adequacy of beta blockade in attenuating the heart rate response to isoproterenol.

In separate studies, the same doses of norepinephrine and isoproterenol were administered intravenously to the goats to measure the effect of these adrenergic agonists on blood pressure and heart rate, respectively, in the absence of adrenergic blockers. Whenever norepinephrine or isoproterenol was infused, blood pressure and heart rate measurements were continuously recorded, and the values obtained after five minutes of infusion were used for data analysis.

Data Analysis

For each CO2 rebreathing curve, minute ventilation ($\dot{V}E$), tidal volume (VT), inspiratory time (Ti), and mean inspiratory flow (VT/Ti) were derived on a breath-by-breath basis. All volume data were expressed at BTPS conditions. Data obtained from the triplicate rebreathing studies performed under a particular experimental condition in each goat were pooled for plotting and statistical analysis (Figure 1). Linear

Fig. 1

regressions were calculated for plots of $\dot{V}E$ and VT/Ti as functions of simultaneously measured PETCO2. Ventilatory responsiveness of each goat to CO2 rebreathing was evaluated from slopes of these curves, from their intercepts on the PETCO2 axis, and from values of $\dot{V}E$ or VT/Ti at PETCO2 = 70 torr.

For statistical analysis, paired t-tests were performed to compare data obtained before and after adrenergic blockade. Data were tested for normality by the Wilk-Shapiro test (Shapiro and Wilk [1965]). A p value <0.05 was considered statistically significant.

Results

The effects of beta blockade on the ventilatory responses to CO2 rebreathing in each of the 5 goats are shown in Figure 2. There was no statistically significant difference in mean values of the slopes, the X-intercepts, or $\dot{V}E$ at PETCO2 = 70 for these lines before and after propranolol for the 5 goats (Table 1). We also assessed ventilatory drive by plotting VT/Ti against PETCO2 for the same CO2 rebreathing tests. Again, there were no statistically significant differences in the mean slopes, the X-intercepts, or VT/Ti calculated from the regression lines at PETCO2 = 70 before vs. after propranolol (Table 1).

Fig. 2

Table 1

To assess the effectiveness of propranolol infusion in blocking beta receptors, we compared heart rate responses to isoproterenol infusion with and without propranolol pretreatment (Figure 3). The mean change in heart rate after isoproterenol was reduced by 86% following administration of propranolol. The mean (±S.E.) baseline heart rate was somewhat lower after

Fig. 3

administration of propranolol (73 ± 10 to 63 ± 7 beats/min), but this difference was not statistically significant.

The ventilatory response to CO2 rebreathing for each of the 5 goats before and after alpha-blockade with phentolamine is shown in Figure 4. There was no statistically significant change in mean values of the slopes, the X-intercepts, or $\dot{V}E$ calculated at PETCO2 = 70 (Table 2). When VT/Ti was plotted against PETCO2, there was a slight but statistically significant decrease in slope and X-intercept. However, there was no difference in VT/Ti calculated from the regression line for PETCO2 = 70 after (compared to before) phentolamine (Table 2).

To assess the adequacy of alpha-blockade, we compared the increase in arterial blood pressure in response to infusion of norepinephrine while the goat was receiving phentolamine with that seen in the absence of alpha blockade (Figure 5). Phentolamine administration did not change the average baseline mean arterial pressure (83 ± 4 before vs. 82 ± 3 mm. Hg after phentolamine), but it did attenuate the pressor response to norepinephrine infusion by 76%.

Discussion

In this study in awake resting goats, we found no significant effect of either alpha or beta adrenergic blockade on the response of minute ventilation or mean inspiratory flow to hyperoxic CO2 rebreathing. That adrenergic receptors were adequately blocked is suggested by the minimal response to relatively large doses of the corresponding agonists.

There are several possible interpretations of the lack of

effect of adrenergic blockade on CO2 responsiveness in goats. First is the possibility that sympathoadrenal activity does not play a role in modulating CO2 responsiveness. The fact that some investigators (Mustchin, et al. [1976]; Trembath, et al. [1979]) have found effects of beta blockade on the ventilatory response to CO_2, whereas we and others (Hutchinson and Harrison [1980]; Patrick, Tutty, and Pearson [1978]) have not, suggests that the answer may not be so straightforward. Other potential effects of adrenergic blockers, such as alteration of CO2 production or of physiologic deadspace, might secondarily affect resting ventilation or the measured response to ventilatory stimuli, and might differ among studies. On the basis of published data, it is difficult to determine whether discrepancies among studies can be explained in part by differences in these other effects.

Second is the possibility that the response to adrenergic blockers depends upon the level of baseline sympathoadrenal activity. Since there was no marked change in mean blood pressure after phentolamine or heart rate after propranolol, it appears that baseline adrenergic tone was relatively low in these goats, perhaps accounting for the absence of a change in CO2 responsiveness after adrenergic blockade.

A third possibility is that adrenergic activity may influence ventilation by altering the output of carotid chemoreceptors in normoxic conditions, but that this influence is suppressed in hyperoxic states (Heistad, et al. [1972]; Winn, Hildebrandt, and Hildebrandt [1979]). Since our studies were all performed under hyperoxic conditions, carotid chemoreceptor

activity was presumably suppressed. This might explain why manipulating adrenergic activity did not influence the ventilatory response to CO2.

Whether adrenergic activity is altered as a result of the hypercapnia induced by CO2 rebreathing cannot be answered without measurements reflecting sympathoadrenal activity, such as norepinephrine turnover or plasma catecholamine levels. However, even if such changes do occur, we do not think they influence ventilatory responsiveness to hyperoxic CO_2 rebreathing in goats, for that was not altered following adrenergic blockade.

We conclude that, in our resting goats, neither basal adrenergic activity nor a change in adrenergic activity (if such occurred during hypercapnia) contributed to the ventilatory responses to CO2 inhalation. Our findings suggest that if the sympathoadrenal system does influence ventilatory responses to CO2 in some mammals, then the goat is not a good species in which to study this relationship. Additionally, if adrenergic activity influences ventilatory drive through the carotid body chemoreceptors, a normoxic or hypoxic test of ventilatory responsiveness might be required to demonstrate such an effect.

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In conducting the research described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals", as prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council.

The views, opinions, and/or findings contained in this report are those of the authors and should not be construed as an official Department of the Army position, policy, or decision, unless so designated by other official documentation.

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TABLE 1

EFFECT OF BETA BLOCKADE ON CO_2 RESPONSE CURVES IN AWAKE GOATS

	MINUTE VENTILATION ($\dot{V}_E$)		
	SLOPE ($L \cdot min^{-1} \cdot torr^{-1}$)	X-INTERCEPT (torr)	$\dot{V}_E$ AT $PETCO_2$=70 TORR ($L \cdot min^{-1}$)
CONTROL	1.77±0.35	54.3±2.0	25.9±3.1
PROPRANOLOL	1.55±0.29	54.1±2.1	23.0±3.4
p	NS	NS	NS

	MEAN INSPIRATORY FLOW (V_T/T_i)		
	SLOPE ($L \cdot min^{-1} \cdot torr^{-1}$)	X-INTERCEPT (torr)	V_T/T_i AT $PETCO_2$=70 TORR ($L \cdot min^{-1}$)
CONTROL	3.84±0.84	52.7±2.0	60.6±7.2
PROPRANOLOL	3.48±0.72	53.1±2.1	54.0±7.2
p	NS	NS	NS

Values are means±SE; n=5.

TABLE 2

EFFECT OF ALPHA BLOCKADE ON CO_2 RESPONSE CURVES IN AWAKE GOATS

MINUTE VENTILATION ($\dot{V}_E$)

	SLOPE ($L \cdot min^{-1} \cdot torr^{-1}$)	X-INTERCEPT (torr)	$\dot{V}_E$ AT $PETCO_2$=70 TORR ($L \cdot min^{-1}$)
CONTROL	1.95±0.40	53.2±2.6	29.6±3.8
PHENTOLAMINE	1.85±0.50	50.9±3.3	29.9±4.6
p	NS	NS	NS

MEAN INSPIRATORY FLOW (V_T/T_i)

	SLOPE ($L \cdot min^{-1} \cdot torr^{-1}$)	X-INTERCEPT (torr)	V_T/T_i AT $PETCO_2$=70 TORR ($L \cdot min^{-1}$)
CONTROL	4.26±0.90	51.9±3.2	68.8±9.8
PHENTOLAMINE	3.78±1.02	48.0±3.9	70.1±11.1
p	<0.05	<0.05	NS

Values are means±SE; n=5.

FIGURES

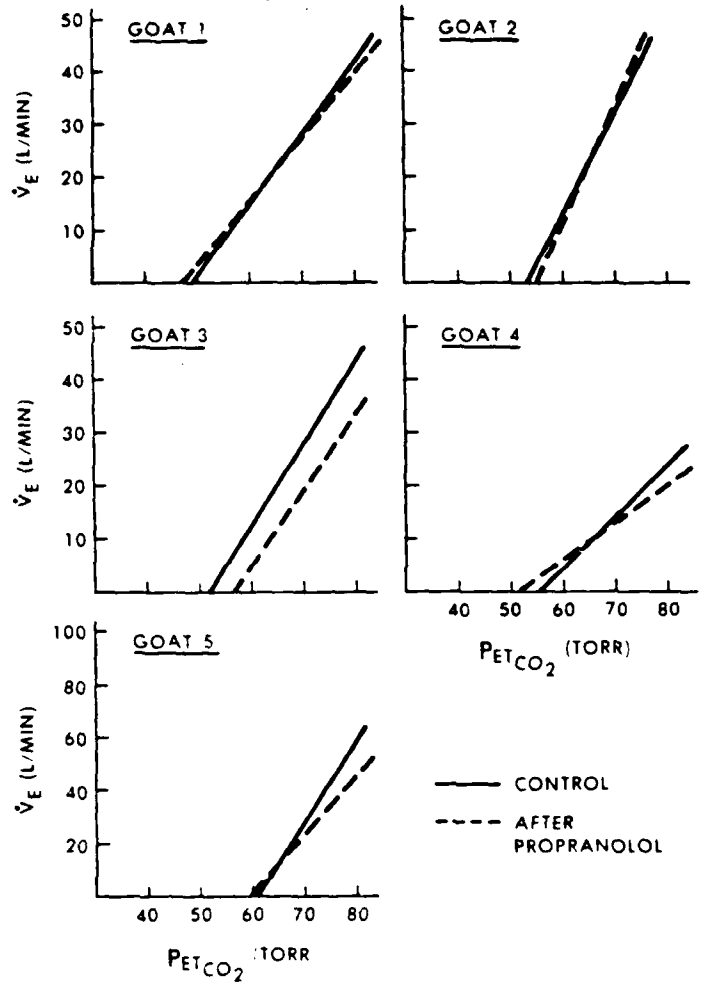
FIG. 1 Representative plot of $\dot{V}_E$ against P_{ETCO2} for repetitive rebreathing studies on a single goat. Individual breaths are plotted; each of the 3 studies is represented by a different symbol. The straight line best fits the pooled data.

FIG. 2 Effect of propranolol on CO_2 rebreathing. The lines relating $\dot{V}_E$ to P_{ETCO2} before and after propranolol administration are shown for each of the 5 goats.

FIG. 3 Effect of propranolol on baseline heart rate (±SE) and the heart rate response to isoproterenol infusion.

FIG. 4 Effect of phentolamine on CO_2 rebreathing. The lines relating $\dot{V}_E$ to P_{ETCO2} before and after phentolamine administration are shown for each of the 5 goats.

FIG. 5 Effect of phentolamine on baseline mean arterial blood pressure (±SE) and the blood pressure response to norepinephrine infusion.


GOAT 1
GOAT 2
GOAT 3
GOAT 4
GOAT 5
$\dot{V}_E$ (L/MIN)
50
40
30
20
10
100
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60
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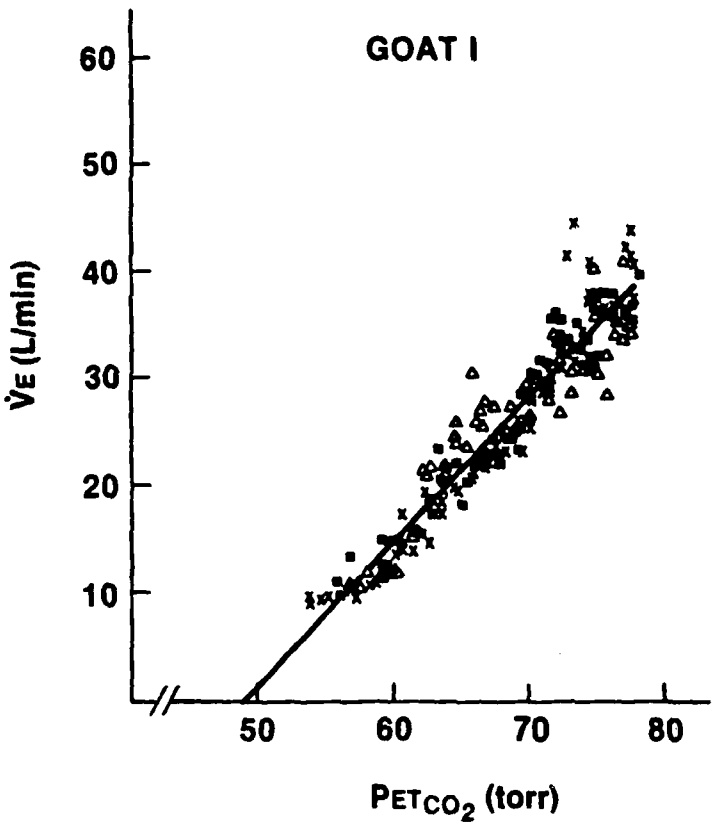
20
40 50 60 70 80
$P_{ET_{CO_2}}$ (TORR)
CONTROL
AFTER PROPRANOLOL


GOAT I
60
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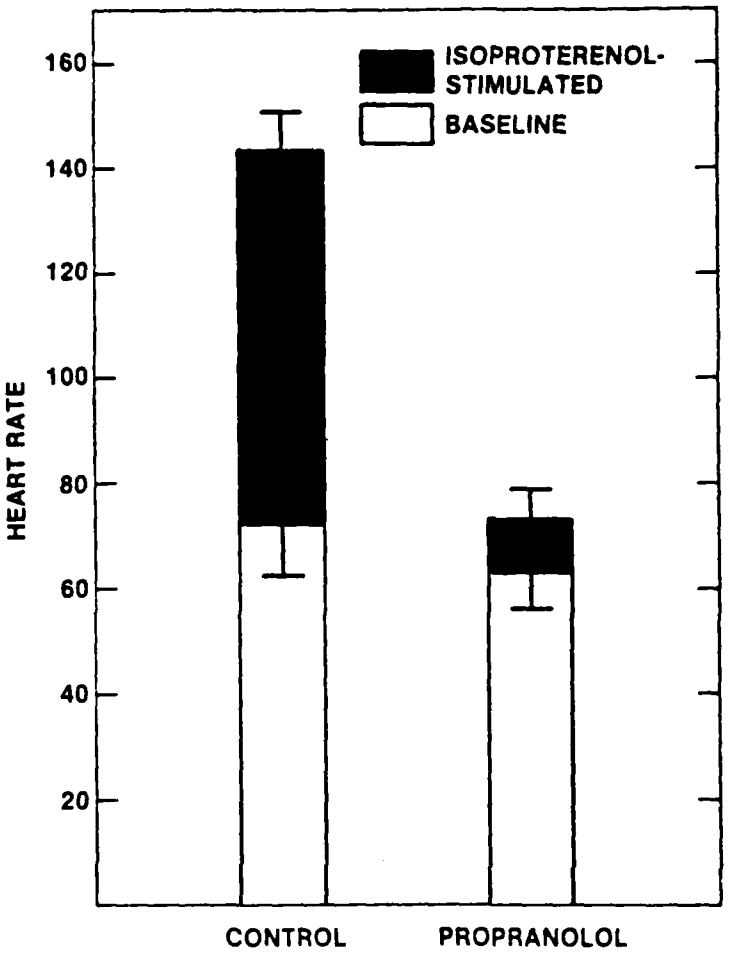
80
$P_{ET}CO_2$ (torr)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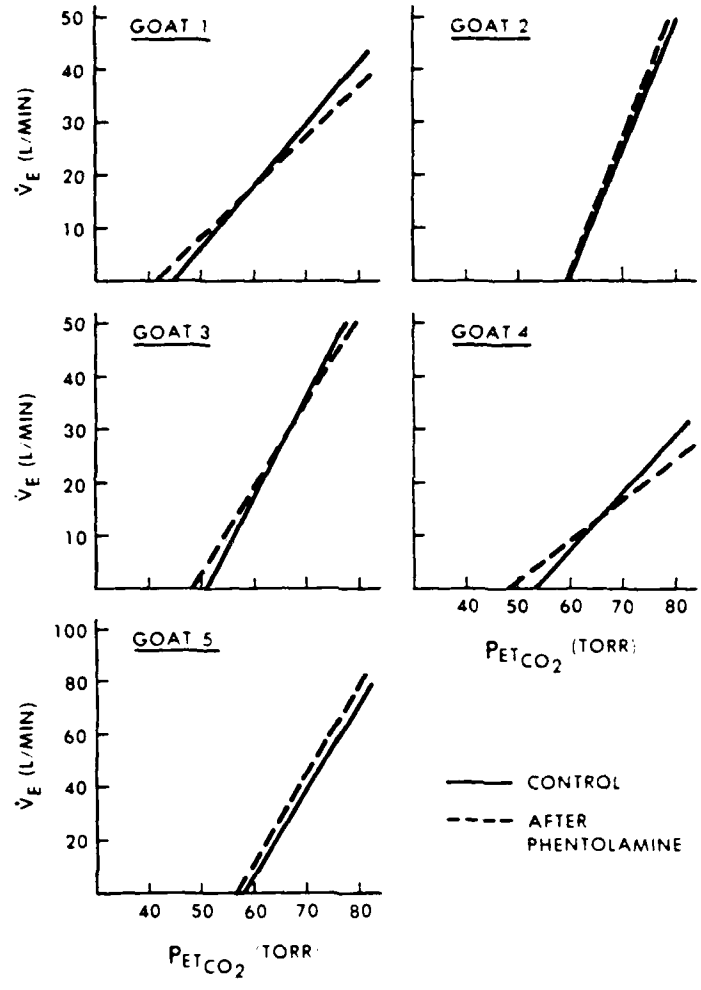
GOAT 1
GOAT 2
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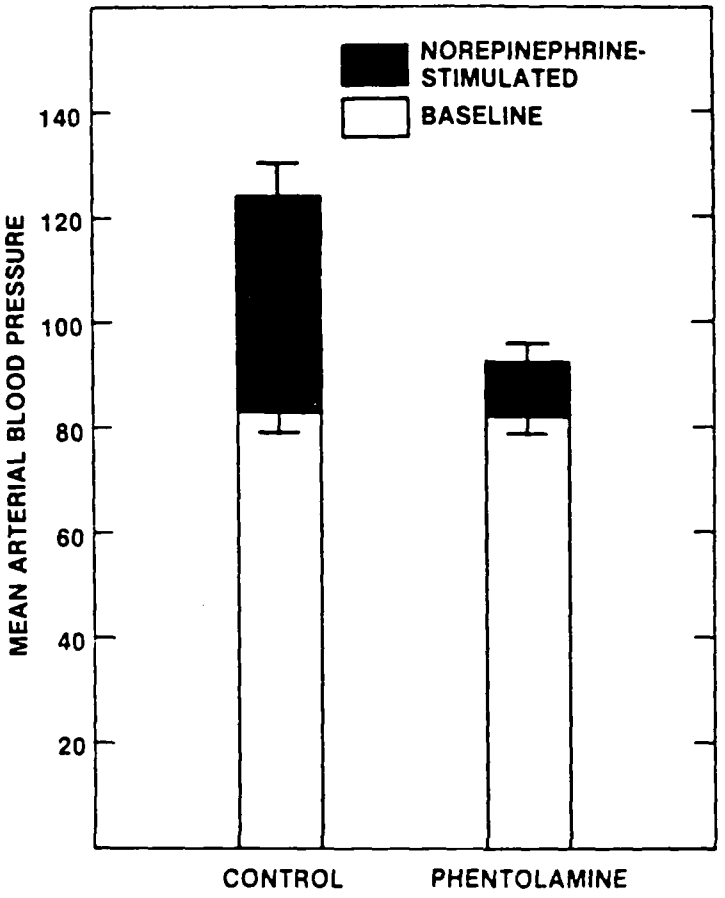
AFTER PHENTOLAMINE


NOREPINEPHRINE-
STIMULATED
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140
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60
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20
CONTROL
PHENTOLAMINE

ANIMAL RESEARCH

In conducting the research described in this report, the investigators adhered to the "*Guide for the Care and Use of Laboratory Animals*," as prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council.

The views, opinions, and/or findings contained in this report are those of the authors and should not be construed as an official Department of the Army position, policy, or decision, unless so designated by other official documentation.

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